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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
STROUP, C	
ART UNIT	**PAPER NUMBER**
1633	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/129,603	Tetsuyoshi Ishiwata et al
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-21 is/are pending in the applicat

Of the above, claim(s) 1 and 18-21 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 2-17 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 12

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claim 1, drawn to proteins, classified in class 514, subclass 2.

II. Claims 2-17, drawn to nucleotides, methods of making and methods of use, classified in class 435, subclass 320.1.

III. Claims 18 -21, drawn to antibodies and methods of use, classified in class 435, subclass 7.1.

2. The inventions are distinct, each from the other because of the following reasons:

The inventions of groups I-III are drawn to compositions having materially different physical and chemical properties, structures, and utilities. For example, the invention of group I is drawn to a polypeptide of SEQ ID NO: 1 that has different characteristics and functions compared to the inventions of groups II and III, which are drawn to polynucleotides and antibodies. Likewise, the structure, function, and utilities of a polynucleotide will be different from those of an oligonucleotide, antibody, and peptide.

3. The inventions of groups I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the polypeptide of group I can be made by chemical synthesis.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their divergent classifictions, recognized divergent subject matter and further because the searches required for the different inventions are not coextensive, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Mr. Lawrence Perry on November 22, 1999 a provisional election was made with traverse to prosecute the invention of Group II, claims 2-17, as pertains to nucleotide sequences, methods of making and using. Affirmation of this election must be made by applicant in responding to this Office Action. Claims 1, 18, and 19 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

7. Claim 8 is objected to because of the following informalities: for the misspelling of "oligonuleotide". Appropriate correction is required.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 10, 11, 14, and 15 are rejected under 35 U.S.C. 101 because the claimed recitation of a method of use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 12-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claimed invention is to a IgA nephropathy diagnostic agent, therapeutic agent and a method for inhibiting expression of a protein as encoded by the amino acid sequences of SEQ ID NO:2 utilizing an oligonucleotide comprising a portion of the nucleotide sequence which encodes the protein of SEQ ID NO: 2, or which comprises a portion of the nucleotide sequence of SEQ ID NO: 1, or comprising a portion of the DNA sequence which hybridizes to the sequence of SEQ ID NO: 1 under stringent conditions.

The specification discloses that IgA nephropathy is a chronic glomerulonephritis of an undetermined etiology for which a fundamental therapeutic method has not been found (pg 1, para 2-pg 2, para 2). The specification also

discloses that approximately 50% of the patients with IgA nephropathy have a high blood IgA level, that there have also been reports of high production of IL-4, 5, and 6, and TGF beta in peripheral T cells of said patients, as well as strong activation of integrins in peripheral lymphocytes (pg 2, para 2). The specification then asserts that: "On the basis of these facts", it is considered that in IgA nephropathy excessive IgA is produced due to an adnormality in the immune system, the resulting IgA deposits on the glomerulus thus activating the complement, which may exert influence and cause disorders of the glomerulus (Pg 3, para 1), and that the present invention provides a novel protein which has been determined to have increased expression levels in leukocytes of IgA nephropathy patients.

The specification fails to provide an enabling disclosure for an IgA nephropathy diagnostic agent because of the lack of a disclosure on the patient profile used on page 43 of the specification as to whether there is any specific criteria or stage of disease the patient must have, such as high IgA levels, for the test to be a reliable diagnostic tool. For example, must the patient be symptomatic by any other criteria for IgA diagnosing for the claimed method to be a reliable test? Is the test able to predict disease prognosis or even susceptibility? Due to the failure of the specification to disclose criteria for patient selection for diagnostic testing, it would require undue experimentation by one of skill in the art to determine the appropriate candidate for testing and the manner in which to analyze the test results.

The specification fails to provide an IgA nephropathy therapeutic, inhibiting agent because of a failure to disclose the role of the protein encoded by SEQ ID NO:2, or the DNA which encodes said protein, or the DNA sequence which encodes SEQ ID NO: 1 or the complement thereof, in the pathophysiology of said disorder or its method of use in any protocol to treat any disorder. The specification discloses an exemplification in which a nucleotide sequence was isolated from a myeloid KG-1 cDNA library, clone KIAA0235 also known as SEQ ID NO: 1, which showed a 100% sequence identity in base pairs 1076-1261 of an unidentified DNA band isolated from the leukocytes of five patients with IgA nephropathy (pg 38, para 2), and that Northern blot of mRNA of KIAA0235 showed that it was expressed 6.6 times more than in control patients (pg 44, lines 1-2). The specification fails to disclose any

assays to ascertain the functional or biological activity of the disclosed sequences, which in fact are as probable for being expressed as a result of the disorder rather than a causative factor, therefore the artisan has no indication that there is any therapeutic value to administering an oligonucleotide to inhibit the expression of the protein encoded by SEQ ID NO: 1.

Additionally, the specification fails to provide an enabling disclosure for a method of inhibiting expression of the protein as encoded by the amino acid sequences of SEQ ID NO:2 because the specification fails to provide essential details in the method of use of antisense oligonucleotide to overcome the high unpredictability in the art. The specification discloses that inhibition of DNA transcription or translation of mRNA can be conducted utilizing an antisense RNA/DNA oligonucleotide sequence of approximately 10-50 sequences (pg 26, para 2). The specification fails to disclose, though, the dose per route of administration, methods of delivery, or the identification of any specific oligonucleotides that have been demonstrated to be stable *in vivo* while effectively inhibiting expression of the protein encoded by SEQ ID NO: 2. For example, S.T. Crooke (Basic Principles of Antisense Therapy) teaches that antisense oligonucleotides, such as phosphorothioate oligonucleotides, are rapidly and extensively absorbed after parental administration, while subcutaneous administration resulted in lower bioavailability and greater distribution to lymph. Their distribution to peripheral tissues also varies depending on the organ, e.g. liver, kidney, bone marrow, skeletal muscle and skin accumulate the highest percentage of the antisense oligonucleotide dose, but other tissues display small quantities of drug. (Crooke, pg 17, para 2 & 3; Plenat full article; Agrawal full article). Therefore, due to the absence of essential teachings within the specification on the method of using any oligonucleotides, such as target tissue, method of targeted delivery, the effective dose and route of administration, one of skill in the art would be required to practice undue experimentation so as to provide any level of therapeutic benefit.

Furthermore, the Applicant is reminded that the unpredictability in the antisense art is largely due to barriers to successful delivery of these molecules to organisms: (1) penetration of the plasma membrane of the target cells to

reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (Branch, pg 45-50). These barriers prevent the oligonucleotides from being distributed and internalized equally among any targeted organs or tissues. Additionally, discovery of antisense molecules with "enhanced specificity" in vivo requires further experimentation for which no guidance is taught within the specification. Note Branch who teaches the state-of-the-art for designing an antisense which inhibits a target in vivo: it "is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense molecules must be found empirically be screening a large number of candidates for their ability to act inside cells." (Branch, pg 49). Due to the absence of teachings within the specification on the specific antisense sequence with a demonstrated ability to inhibit the *in vivo* expression of the protein encoded by SEQ ID NO: 2, or that the ability to do so would in any way inhibit the progression IgA nephropathy, it would require undue experimentation by one of skill in the art to practice the claimed invention such that any therapeutic effect would be achieved.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 2, 4, 7, 10, 11, 14, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is unclear because it depends on a "non-elected" claim.

Claim 4 is unclear as to the metes and bounds of "under stringent conditions" because the conditions are not defined.

Claim 7 is unclear as to the meaning of "the protein according to claim" because of the failure to specify which claim it is referencing.

Claims 10 and 11 are unclear as to the method by which mRNA is derived from protein.

Claims 10, 11, 14, and 15 are unclear due to the absence of steps for the method of using oligonucleotides to detect mRNA and to inhibit protein expression.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 2 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagase et al (7/97).

Applicant's claimed invention is to a DNA encoding a protein of the amino acid sequence represented in SEQ ID NO: 2 ; DNA which comprises the nucleic acid sequence of SEQ ID NO: 1; a vector comprising a recombinant DNA of SEQ ID NO: 1; and a process for making a protein and a transformant obtained by introducing said vector into a host cell.

Nagase et al teach a nucleic acid sequence with 100% identity to the nucleic acid sequence of SEQ ID NO:1 (Accession no. D87078) and the method of obtaining said sequence from cDNA libraries of clones derived from human immature myeloid cell line KG-1. Therefore, the claimed invention was clearly anticipated.

Applicant cannot rely upon the foreign priority to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

16. Claims 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Biolabs, Inc (1988).

Applicant's claimed invention is to an oligonucleotide comprising a portion of a nucleotide sequence of the DNA comprising the nucleotide sequence of SEQ ID NO:1, or that which hybridizes to it.

BioLabs Catalog discloses a random primer which hybridizes to any known DNA sequence (#1230). Therefore, the claimed invention was clearly anticipated.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase et al (7/97) in view of Kendrew et al (1994) and Bresser et al (US Patent 5,225,326).

Applicant's claimed invention is to an oligonucleotide and a method of use in detecting mRNA derived from the protein comprising the amino acid sequence represented by SEQ ID NO:2, using an oligonucleotide comprising a portion of the nucleotide sequence of SEQ ID NO:1 or a complementary portion thereof.

Nagase et al teach a nucleic acid sequence with 100% identity to the nucleic acid sequence of SEQ ID NO:1 (Accession no. D87078), as well as an amino acid sequence with 100% identity to the amino acid sequence of SEQ ID NO: 2 (Accession no. O00234). Nagase et al does not teach hybridization techniques.

Kendrew et al teach the use of nucleic acid hybridization, such as for the use of detecting mRNA in northern blots (pg 503-505).

Bresser et al teach the method of making and using oligonucleotide hybridization probes (col 11, lines 20-65; col 13, lines 15-60).

In light of Nagase, Kendrew and Bresser et al, it would have been obvious to one of ordinary skill in the art to utilize an oligonucleotide sequence comprising a portion of the DNA sequence of SEQ ID NO: 1, or a complementary portion thereof, to bind to mRNA derived from the protein encoded by SEQ ID NO: 2. One would be motivated to do this to analyze the presence of said mRNA to study the differential expression of specific genes in response to particular stimuli (Kendrew et al, pg 505, col 1, para 2). There would be a reasonable expectation of success because said use of Northern blots is a standard in the art of molecular biology.

Applicant cannot rely upon the foreign priority to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasmine Chambers, can be reached at (703) 308-2035. The fax phone number for this Group is (703) 308-0294.

Carrie Stroup

Bruce Campell

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